Change to the Specification

The above mentioned change to the specification at page 5, Table 1 is to correct an obvious error in preparation of the Table. As can be seen, the data of Table 1 provides support for the change of the compound 11 5-HT_{1A}/5-HT_{1D} IC_{50} binding ratio from 65.6 to 265.6. This ratio was calculated by dividing the 5-HT_{1A} IC_{50} value for compound 11 in column 4 of the Table (850 ± 40) by the 5-HT_{1D} IC_{50} value for compound 11 in column 3 (3.2 ± 0.3). As is apparent, this calculation results in a 5-HT_{1A}/5-HT_{1D} IC_{50} of 265.6 instead of 65.6 as was mistakenly presented.

Abstract

The Examiner has asked for an abstract of the Disclosure. A suitable abstract is herewith attached. This is the Abstract used in the application during the International Phase.

REMARKS

Original Claims 1-9 were rejected in parent application 08/211,446. Reconsideration of the Official Action dated December 9, 1994 is respectfully requested in view of the amendments and submissions now filed.

I. Claims 1-9 have been rejected under 35 U.S.C. § 112, second paragraph. Claim 1 has been cancelled and replaced by new claim 11. Claim 11 corresponds to original claim 1 with the following exceptions:

(1) the alkyl groups are stated to be C_{1-6} alkyl groups;

(2) the possibility of "Z" having the formula (III) or (IV) has been excluded; and

(3) the last line refers to salts in the alternative.

In response to the Examiner's specific points:

(1) Claim 11 no longer contains any reference to a R^5 NHCO group.

(2) The Examiner's suggested amendment to the last line of claim 1 has been made and claim 5 has been deleted.

(3) The spelling of "pyrrolidine" has been corrected in claim 4. Basis for the correction is found in the specification on page 8, line 8.

(4) Claim 8 has been deleted and the reference to migraines has been deleted from claim 9. This limitation has been made the subject matter of new dependent claim 10.

II. Claims 7 and 8 have been rejected under 35 U.S.C. § 101. These claims have been deleted.

III. The specification has been objected to and claims 1 to 3 and 5 to 9 have been rejected under 35 U.S.C. § 112, first paragraph. In the claims the "alkyl" group is now indicated to be a "C_{1-6} alkyl" group. Basis for this amendment is found in the specification on page 2, lines 28-30. Accordingly, the references to "C_{1-6} alkyl" now in claim 11 no longer include all carbon chain lengths.

In new claim 11 references to Z representing a ring formula (III) or (IV) have been deleted. Thus Z can now only represent a ring of formula (II) or (V). Test data are given in the specification for compounds 1, 2 and 11. These are compounds where Z is a group of formula (II) in which n is 4 or 5 or wherein Z is a group of formula (V) in which R^6 is an ethyl group. It is respectfully submitted that these data are sufficient to provide a reasonable assurance to a person of ordinary skill in the art that the claimed compounds are useful and have the activity ascribed to them.

IV. Claims 1 to 4 and 6 to 9 have been rejected under 35 U.S.C. § 103 as being unpatentable over Bays et al. in view of Oxford et al.. The Examiner asserts that Bays et al. teach indoles and the use of said compounds in treating headaches. The compounds of Bays et al. are held to differ from those claimed in that the Bays et al. compound have a

carbonyl group vs. the instant sulfonyl group linking the indole alkyl residue and nitrogen hetero rings.

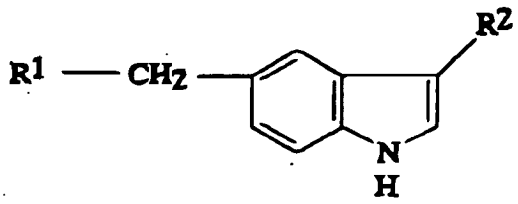
Oxford et al. are held to teach that both carbonyl and sulfonyl groups are viable moieties. The Examiner then asserts that it would have been obvious to one of ordinary skill in the art to substitute the carbonyl moieties of Bays et al. with sulfonyl groups to produce compounds with the same or equivalent properties.

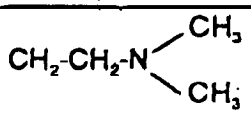
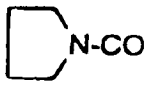
It is respectfully submitted that the object of the present invention was to produce compounds which have superior a selective binding affinity for the 5-HT_{1D} receptor. The claimed compounds meet this objective. They have a high binding affinity for the 5-HT_{1D} receptor. This affinity is significantly greater than their affinity for the 5-HT_{1A} receptor. The ratio of biding affinities for the 5-HT_{1A}/5-HT_{1D} receptors is surprisingly significantly larger for the compounds of the instant claims than for the compounds of the Bays et al. reference.

In order to demonstrate the differences in binding affinties a comparative test has been carried out. These results are presented in the declaration of Dr. Fernandez which will be submitted forthwith. As can be seen from the declaration and specification, the 5-HT_{1A}/5-HT_{1D} IC_{50} binding ratios for compounds 1 and 11 of the present invention/claims

have already been measured. These are set out in Table 1 on page 5 of the specification. The 5-HT_{1A}/5-HT_{1D} IC_{50} ratio for compound 1 is 77.1. The ratio for compound 11 is 265.6. As set forth above, this is the correct ratio arrived at by dividing the 5-HT_{1A} IC_{50} value by the 5-HT_{1D} IC_{50} value given in columns 3 and 4 of Table 1, respectively. The same tests set out on pages 3 to 5 of the specification were carried out for the two compounds set forth in the Bays reference which have a carbonyl group linking the indole alkyl residue and nitrogen hetero rings. These compounds were chosen to provide binding results that can be directly compared with the binding results of compounds 1 and 11 of the instant claims. Thus, the compounds chosen are identical to the compounds 1 and 11 of the instant invention, except for the replacement of the SO_2 group by a CO group. All of the active compounds disclosed in Bays et al. contain a CO or CS group in the position occupied by the SO_2 group in the compounds of the instant invention. Thus, what were tested were the most similar compounds within formula (I) of Bays et al. to the compounds of the present invention.

The results obtained are set forth in the Table on the following page:



Compound	R^1	R^2	M.P. °C	^{125}I-GTI	^{3}H-8-OH-DPAT	5-HT_{1a} / 5-HT_{1b}
Compound 1			218-20(*)	10.7	825	77.1
Bays A		"	156-7(**)	88	503	5.7
Compound 11		"	170-1	3.2	850	265.6
Bays B		"	135-7	48	669	13.9

(*) Hydrochloride (**) Hydrogen fumarate

By comparing compound 1 with compound A of Bays et al., it can clearly be seen that the substitution of the CO group of Bays et al. with an SO_2 group in accordance with the instant invention leads to a dramatic and unexpected increase in the 5-HT_{1A}/5-HT_{1D} IC_{50} ratio from 5.7:1 to 77.1:1. Similarly, a corresponding substitution for compound 11 and the Bays et al. compound B provides an increase in the ratio of from 13.9:1 to 265.6:1. These considerable increases in the 5-HT_{1A}/5-HT_{1D} IC_{50} ratios could not have been foreseen from either the Bays et al. or Oxford et al. references. In fact, Bays et al. teach nothing as to the use of a sulfonyl group instead of a carbonyl group to link the indole alkyl residue and the nitrogen hetero ring. Further, Oxford et al. merely mention that <u>in their compounds</u> the group represented by "D" could be either -CO- or -SO_2-. Oxford appear to treat the CO and SO_2 groups as equivalents and make no mention of any functional difference between the two. Oxford et al. provide no teachings, nor do they mention that the substitution of the CO for the SO_2 group in compounds such as those of Bays et al. would produce dramatic changes in the binding affinity of said compounds for the 5-HT_{1A} and 5-HT_{1D} receptors. It is respectfully submitted that in view of this surprising and advantageous effect, the rejection under 35 U.S.C. § 103 should be withdrawn.

V. Claim 5 has been rejected under 35 U.S.C. § 103 as being unpatentable over Sundberg et al.. Without admitting the correctness of this rejection, claim 5 has been cancelled.

Favorable consideration of the above identified application in light of the above amendments is respectfully requested.

Should the Examiner believe a conference would advance the prosecution of the application, the Examiner is encouraged to telephone the undersigned counsel to arrange a conference.

Respectfully submitted,

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